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What Proportion of Patients with Heart Failure and Left Ventricular Ejection Fraction 40-49% Fulfil the Criteria for Heart Failure with Mid-Range Ejection Fraction?

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24th July 2018

Dear Professor William Roberts,

What proportion of patients with Heart Failure and LVEF 40-49% fulfil the criteria for Heart Failure with mid range Ejection Fraction?

Thank you for taking the time to review our research letter to the American Journal of Cardiology.

The updated 2016 ESC heart failure guidelines were intended to simplify diagnosing patients and a new category, Heart Failure with mid range Ejection Fraction (HFmrEF) was introduced. However, our research has shown that there is a small number of patients that have heart failure symptoms, raised natriuretic peptides and impaired left ventricular ejection fraction (LVEF: 40-49%) but without structural heart disease or diastolic dysfunction. This means that these patients have heart failure but do not fit into the new guidelines. From our research, we believe these patients may have a better outcome, with none of these patients experiencing deteriorating LVEF during follow up. This distinction is important; as it is likely that one size does not fit all for HFmrEF patients.

I can confirm that all authors have participated in the work and have reviewed and agree with the content of the article. None of the article contents are under consideration for publication in any other journal or have been published in any journal. No portion of the text has been copied from other material in the literature.

Yours faithfully,

Dr Jessica Webb

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29th August 2018

Dear Professor William Roberts,

What proportion of patients with Heart Failure and LVEF 40-49% fulfil the criteria for Heart Failure with mid range Ejection Fraction?

We are pleased to submit our revised manuscript for publication in AJC. We thank you for you thoughtful comments and have amended our manuscript in accordance with their recommendations.

I confirm that all authors have contributed significantly to this work, that this work is not under consideration elsewhere and that there are no conflicts of interest.

Yours faithfully,

Dr Jessica Webb

Response to the Reviewers comments

- Incorporate my editorial changes into your revision (See copy marked "WCR" to be found under 'Action Links' 'Manage Review Attachments.').

  This has been done.

- I altered your title by spelling out "LVEF" (see above); additionally, the first letter of each major word in the title should be in capital letters (see above). This has been changed

- All paragraphs should be fully indented. This has been changed

- Your references need major attention (see copy marked 'WCR"): they should be double spaced; the names of all authors are required in every reference (do not use 'et al'); the names of the referenced journals should be in italics; proper abbreviations should be used for the names of all referenced journals; periods should not be placed after the name of any referenced journal; full inclusive pages are needed in every reference (140-149 not 140-9). Your figure should be in a separate file attached after the manuscript. Thank you. This has been modified

What Proportion of Patients with Heart Failure and Left Ventricular Ejection Fraction 40-49% Fulfil the Criteria for Heart Failure with Mid-Range Ejection Fraction?

Running title: **Fulfilling diagnostic criteria in HFmrEF**

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Competing Interests

The authors declare that they have no relevant disclosures or competing interests

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Word Count 1646

The ESC updated guidelines introducing Heart Failure with mid range Ejection Fraction (HFmrEF) were not validated prior to publication [1]. The relative importance of stuctural heart disease or diastolic dysfunction in diagnosing HFmrEF is not known. Moreover, the exact prevalence remains unclear largely because different LVEF have been used to define these 'grey area' patients [2-4].

The aim of this study was to establish the clinical impact of these guidelines. All consecutive patients admitted to hospital with HF were recruited over a 12 month period (follow up: 26.8 months, range 22.1-34.0). A diagnosis of new HF was made by an expert physician and patients were categorised with structural heart disease and/or diastolic dysfunction, and so whether they reached the ESC criteria for HFmrEF. Patients were ≥18 years of age and were included if in New York Heart Association (NYHA) functional class II-IV.

In total, 677 patients had a new diagnosis of HF, of which 142 patients (21%) were identified with LVEF 40-49%; but only 88.7% satisfied the ESC criteria for HFmrEF with evidence of diastolic dysfunction and/or structural heart disease. 66 patients had left atrial enlargement, 64 patients had left ventricular hypertrophy, 81 patients had e' <9cm/s and 51 patients had E/e' ≥ 13. In total, 16 patients (11.3%) were admitted with heart failure, raised NTproBNP and LVEF 40-49% but with no evidence of diastolic dysfunction and/or structural heart disease, and so were not categorised as HFmrEF, Figure 1.

These 16 patients were more likely to be male (p 0.02), anaemic (p 0.03), iron deficient (p 0.04) and have more comorbidities (p 0.01) than the patients who fulfilled the HFmrEF criteria. Follow up was 100% complete. There was no difference in all

cause death (0.15) or HF hospitalisation (p 0.33) between the true and the HFmrEF patients without structural heart disease or diastolic dysfunction. Despite comparable medical therapies, fewer of the patients without true HFmrEF transitioned to HFrEF, compared to those 'true' HFmrEF patients (p 0.05).

The diagnostic criteria for HFmrEF have never been validated in clinical studies and our data suggests that implementing this classification ignores a subset of patients. This is the first publication on HFmrEF that has separated out patients with HF and LVEF 40-49% into true 'HFmrEF' patients and HF LVEF 40-49% without structural heart disease or diastolic dysfunction. This distinction is important as it is likely that one size does not fit all for HFmrEF patients, and that there is a cohort of 'ignored' patients without structural heart disease or diastolic dysfunction that can be easily defined.

The benefit of this updated ESC classification must be called into question. These patients are not a new population [5] but rather one that have been poorly described previously and current efforts have not improved the situation. Current estimates worldwide are that there are 26 million patients with HF, more than the entire population of Australia [6]. Extending this worldwide analogy, there are the same number of patients with HFmrEF as the entire population of Singapore. With such large numbers, more work is needed to understand this population and the accuracy of the diagnostic criteria.

Dr Jessica Webb, PhD, Jane Draper, Gerald Carr-White PhD; Guys and St Thomas' NHS Foundation Trust, London, United Kingdom

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M, Document R. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;Aug;18:891-975.

2. He KL, Burkhoff D, Leng WX, Liang ZR, Fan L, Wang J, Maurer MS. Comparison of ventricular structure and function in Chinese patients with heart failure and ejection fractions >55% versus 40% to 55% versus <40%. *Am J Cardiol* 2009;103:845-851.

3. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Investigators C, Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;362:777-781.

4. Gottdiener JS, McClelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, Cushman M, Polak J, Gardin JM, Gersh BJ, Aurigemma GP, Manolio TA. Outcome of congestive heart failure in elderly persons: influence of left ventricular

systolic function. The Cardiovascular Health Study. *Ann Intern Med* 2002;137:631-639.

5. Lam CS, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%). *Eur J Heart Fail* 2014;16:1049-1055.

6. Ambrosy AP, Gheorghiade M, Chioncel O, Mentz RJ, Butler J. Global perspectives in hospitalized heart failure: regional and ethnic variation in patient characteristics, management, and outcomes. *Curr Heart Fail Rep* 2014;11:416-427.

Figure 1: All HF patients with LVEF 40-49% and either diastolic dysfunction or evidence of structural heart disease